

REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 1-78 and 98-109 were cancelled previously. Claims 79 and 80 have been amended. Claims 79-97 and 110-115 are in the case and are before the Examiner.

I. The Amendments

Claims 79 and 80 have been amended to recite a sequence variation of no more than about 5 percent. Support for these amendments can be found at least at page 47 of the specification.

Claim 79(b) has been amended to clarify the meaning of the bracketed phrase by rearranging the position of the words.

Each of the claims has also been amended to recite the conditions under which the chimer particles enhanced stability is measured. Specific support for these amendments can be found throughout the application as in the first full paragraph of the Summary bridging pages 7 and 8, the first of the benefits and advantages on page 12, the descriptions of Figs. 3, 4 and 8, the first full paragraph of the detailed description and in Example 6B that bridges pages 126-127.

Claim 80 has been amended to remove recitation of a chimer that has no inserted residue(s) in the immunogenic loop. Support for this amendment can be found at least in the first paragraph of page 25. Claim 80 has also been amended to recite that the substituted residue(s) are conservative substitutions. Support for this amendment can be found at least in claim 79.

It is thus seen that no new matter has been added.

II. The Action

A. Rejections Under 35 USC §112,
First and Second Paragraphs

Withdrawal of the rejections under the first and second paragraphs of Section 112 is noted with appreciation.

B. Rejections Under 35 USC §102

Withdrawal of the rejections for anticipation under Section 102 is noted with appreciation.

C. Rejections Under 35 USC §103(a)

- (1) Ireland In View of Zlotnick
- (2) Zlotnick in view of Pumpens
- (3) Thornton in view of Zlotnick

All of the presently pending claims were rejected as allegedly obvious from one or more of the above combinations of teachings. Each of these rejections suffers from the same hindsight reconstruction fault, and is respectfully traversed. Because of the commonality of error in the bases for rejection, the rejections will be dealt with together after a brief review of the teachings of each document.

Ireland teaches the insertion of a peptide sequence from the inhibin molecule into the HBC molecule at one of two positions. The first is at the C-terminal position of a truncated HBC whose C-terminal final HBC residue is residue 144, whereas the other construct places the inhibin peptide within the sequence of the full-length core polypeptide at position 78. Thus, the former chimera contained no C-terminal Cys, whereas the latter contained a Cys at position 183 or 185, depending on which strain of HBV was used.

The Zlotnick paper teaches two polypeptides that might be of interest to this discussion. The first is designated Cp*149 and contains HBC residues 1-149 in which each of the native Cys residues that are present at positions 48, 61 and 107 was replaced by an Ala residue, and a similar construct denominated Cp*150 that further contained an added C-terminal cysteine. Neither construct contained an added, heterologous epitope as is claimed here. Zlotnick neither says nor suggests anything about the effect of a C-terminal cysteine on a truncated HBC molecule that has its internal cysteines nor such a molecule that has an inserted sequence.

Pumpens teaches that "capsids formed by C-terminally truncated HBC monomers are less stable than the corresponding full-length protein particles." That statement was echoed by the later-published Borisova paper [*Intervirology* 39:16-22 (1999); provided with the prior Reply and noted on that Form PTO 1449] that states near the top of the right-hand column of page 18 "HBC Δ (C-terminally-truncated HBC particles) were less stable than the corresponding full-length protein particles." Those teachings are agreed with and echoed in the present application.

However, great weight is placed on the Pumpens disclosure that foreign insertions internal to the sequence "also exert an stabilizing effect on chimeric HBC Δ (sic) derivatives" even though the basis for that statement is unpublished work by Borisova whose later-published paper dealt with such internal insertions into HBC, but reported no enhancement of stability.

Thornton teaches that one can link a peptide into HBC and according to the Action, one can thereby obtain a claimed construct with the help of the Zlotnick teachings.

It is noted that all of the claims recite that the substitutions present are conservative. It is respectfully submitted that an Ala for Cys substitution taught by Zlotnick is not "conservative", and that being the case, the Zlotnick teaching is not properly combinable with any other relied-on disclosure.

Thus, when combined with Ireland, one must C-terminally truncate the construct used by Ireland and if one put Ireland's peptide into Zlotnick's Cp*150 construct there would be non-conservative substitutions at positions 48, 61 and 107. A similar result occurs when the Pumpens and Zlotnick teachings are combined. When one studies Thornton, one finds that the inserted sequence can be placed almost anywhere in the HBC sequence. It is submitted that that disclosure is so diffuse as to be of no use to any worker without undue experimentation as to what would work and form particles. Even if one were to combine the teachings of Thornton and Zlotnick, the same result would occur as happened with the combinations of

Zlotnick and either Pumpens or Ireland; i.e., a construct not within those encompassed by the claims.

There are inadequate sign posts in those teachings to lead a skilled worker to the claimed subject matter. Rather, the only way a worker of any skill level could come up with a claimed construct is to read this disclosure and then revise those other teachings to conform to what is taught here.

Thus, in a broader sense, the present and prior Actions have selected from the art only so much as would seem to make a *prime facie* case based on a hindsight reconstruction of the claimed subject matter, while neglecting to examine the teachings of the art as a whole, as is required by the Court in *Panduit Corp. v. Dennison Manufacturing Co.*, 227 USPQ 337, 344-345 (Fed. Cir. 1985) and the cases cited therein. As the Court said,

[i]n its consideration of the prior art, however, the district court erred . . . in considering the claims in less than their entireties . . . and in considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand. . . .

* * * * *

The result is that the claims were used as a frame, and individual naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention. [Quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 USPQ 303, 311-312 (Fed. Cir. 1983).]

Turning more specifically to the asserted rejections, great weight has been placed on the Pumpens disclosure that foreign insertions internal to the sequence "also exert an stabilizing effect on chimeric HBC Δ (sic) derivatives" even though the basis for that statement is unpublished work by Borisova whose later-published paper dealt with such internal insertions into HBC, but reported no enhancement of stability. The present Action asserts that the Pumpens paper was a

written record. Any published statements, suggestions, opinion, written records, etc, reflect the state of the prior art and knowledge of one of skill in the art, and can be used for assessing the obviousness of an invention at the time the invention was made. (Action, page 6, Paragraph 20.)

Unfortunately, that argument here is misplaced. It is submitted that that Pumpens/Borisova disclosure of stabilization through internal insertion is actually helpful here because it leads away from the present invention whose active agent gains stabilization from an added C-terminal cysteine.

In addition, the argument is also misplaced because the present disclosure and claims are directed to those of skill in the art. It is submitted that a skilled worker here has a PhD or MD degree, or both, several years of experience as a leader of a research group of several advanced degreed workers, and has published several papers as a sole or lead author. Such people tend to not believe work that is attributed to a worker who, having the opportunity, failed to corroborate the assertion made by another. That is particularly the case where such a worker can examine the data in this application and make up

his/her own mind about the veracity of the statement from another set of data.

Still further, the Schödel papers discussed in the paragraph bridging pages 6 and 7 of the specification (IDS documents A15 and A27) note the instability observed with C-terminally-truncated HBC proteins that contain insertions in their sequences as is claimed herein. Those papers were published in refereed journals and should be given greater weight than Pumpens' aside to Borisova. As was noted previously, if Pumpens/Borisova were correct, the problem of instability would have been solved by inserting foreign sequences. At the least, there are conflicting teachings and each disclosure "must be considered 'for its power to suggest solutions to an artisan of ordinary skill. . . . considering the degree to which one reference might actually discredit another'" [Medichem S.A. v. Rolabo S.L., 77 USPQ2d 1865,1870 (Fed. Cir. 2006) citing *In re Young*, 18 USPQ2d 1089 (Fed. Cir. 1991).]

Of course, had the instability problem been solved as suggested by the Action or as suggested by Pumpens, the problem alluded to in the application at page 7 and noted in Ulrich et al., *Adv. Virus Res.*, vol.50 (1998) Academic Press pages 141-182 (IDS document A28), concerning "the requirement of reproducible preparation of intact chimer particles that can also withstand long-term storage" would have been met and Ulrich, writing three years after Pumpens, would have been mistaken. Ulrich cites the relied-on Pumpens paper, but still notes that stability of truncated, chimeric particles is missing in the art. Indeed, at page 164, Ulrich states:

[t]he stability of chimeric HBcAg particles under storage conditions has not been analyzed in detail; whereas C-terminally truncated HBcAg particles were reported to require storage at -70°C to preserve stability . . . (Citation omitted.)

The Examiner's attention is also invited to the paper by Zhou and Standring that was cited in the prior Action. That paper, Zhou et al., *J. Virol.* **66**(9):5393-5398 (Sept 1992; hereinafter Zhou), discussed results obtained with full length HBC whose four native Cys residues were exchanged for Ala residues, as well as similarly Ala-for-Cys mutated C-terminal-truncated constructs ending with residues 149 and also 172. That paper reported that

Cys residues and disulfides are not required for the assembly of either HBV capsids or the dimers that provide the precursors for capsid assembly. . . . Cys residues stabilize isolated p21.5 structures, as evidenced by the marked reduction in stability of Cys-minus dimers and capsids . . . (Abstract)

The Zhou paper thus is substantially similar in its disclosures to the disclosures of Zlotnick in regard to the effect of the Cys residues on stability of particular constructs, although Zlotnick did not cite the Zhou paper. The relied-on Pumpens paper cited Zhou as did the above Ulrich paper. The Zhou and Zlotnick papers were also cited in an otherwise redundant review by Pumpens and Grens, *FEBS Letters*, **442**:1-6 (1999), enclosed as Exhibit 1 and noted on Form PTO/SB/08A.

Notwithstanding the fact that skilled workers Pumpens and Ulrich not only knew of the Zhou and Zlotnick papers, but cited them, neither group of skilled worker authors put together the earlier Pumpens paper with either of those disclosures to solve the problem of stability as has the present inventor. Here were workers of at least ordinary skill in this art, if not greater than ordinary skill, and they did not do what the Action has asserted would have been obvious to a mere worker of ordinary skill.

It is submitted that once the disclosures of the art as a whole are taken into account, the aside to the Borisova unpublished work would be given little weight by a skilled worker, or if not all together disregarded, that disclosure would have been found confusing and non-directional in view of the contrary disclosures of Ulrich and Schödel. Such a worker would still be looking for an answer to stability when the claimed invention was made and this application was filed. It is further submitted that the only way a worker of any skill in this art would have come to the presently claimed invention would have been by a hindsight reconstruction after reading the present specification and claims. Such a hindsight reconstruction is impermissible in assessing patentability under Section 103, and this rejection should be withdrawn.

D. Provisional Double-Patenting Rejection

Withdrawal of the provisional double-patenting rejection in view of the filed Terminal Disclaimer is noted with appreciation.

Serial No.: 10/806,006

III. Summary

Claims 79 and 80 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

A Petition for an Extension of Time of one month and its required fee as a large entity are enclosed to permit the Examiner extra time to consider this paper.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 
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Enclosures

Form PTO SB/08A, art
Petition and Fee for One-Month Extension of Time

Serial No.: 10/806,006



CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: MAIL STOP AF, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on September 19, 2006.

By

A handwritten signature in black ink, appearing to read "Edward P. Gamson". It is positioned above a horizontal line.

Edward P. Gamson